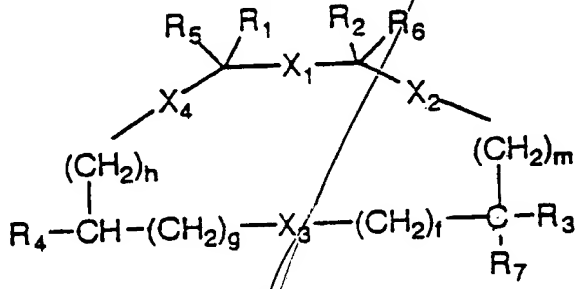
CLAIMS

1. Monocyclic compounds having the general formula (I):



(I)

in which:

X_1, X_2, X_3, X_4, which may be the same or different from one another, represent a group chosen from among -CONR-, -NRCO-, -OCO-, -COO-, $-CH_2NR-$, $-NR-CH_2-$, CH_2-CH_2, where R is H or a C_{1-3} alkyl or benzyl;

f, g, h, m, which may be the same or different from one another, represent a number chosen from among 0, 1 or 2;

R_1 and R_2, which may be the same or different from one another, represent a $-(CH_2)_r-Ar$ group, where r = 0, 1, 2 and where Ar is an aromatic group chosen from among: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, and benzo-imidazole, the said Ar group being possibly substituted with a maximum of 2 residues chosen from among C_{1-3} alkyl or halo-alkyl, C_{1-3} alkoxyl, C_{2-4} amino-alkoxyl, halogen, OH, NH_2, $NR_{13}R_{14}$ where R_{13} and R_{14}, which may be the same or different from one another, represent hydrogen or C_{1-3} alkyl;

R_3 represents a group chosen from among:

- hydrogen
- linear or branched alkyl having the formula C_nH_{2n+1}, with n = 1-5, cyclo-alkyl or alkylcyclo-alkyl groups having the formula C_nH_{2n-1} with n = 5-9
- $(CH_2)_r-Ar_1$, where r = 0, 1, 2 and where Ar_1 is an aromatic group chosen from among: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, and benzo-imidazole, the said Ar_1 group being possibly substituted with a maximum of 2 residues chosen from among C_{1-3} alkyl or halo-alkyl, C_{1-3} alkoxyl or amino-alkoxyl, halogen, OH, NH_2, $NR_{13}R_{14}$, where R_{13} and R_{14}, which may be the same or different from one another, represent hydrogen or C_{1-3} alkyl;

R_4 represents a group chosen from among:

- hydrogen or C_{1-6} alkyl
- L-Q, where L is a chemical bond or a linear or branched C_{1-6} alkyl residue and Q is a group chosen from among:

i) H, OH, OR_9, NH_2, NR_9R_{10}, guanidine, sulphate, phosphonate, phosphate, where R_9 and R_{10}, which may be the same or different from one another, represent a hydrogen, C_{1-3} alkyl group, C_{1-3}hydroxyalkyl, C_{1-3}dihydroxyalkyl, C_{1-3}alkyl-$CONHR_{12}$, C_{1-3}alkyltetrazole, C_{1-3}alkyl-COOH or wherein R_9R_{10} joined together form with the N-atom a saturated 4-6 membered heterocycle possibly containing a further heteroatom chosen in the group consisting of N, O, S and wherein R_{12} is a mono-, di-, tri-glycosidic group possibly protected with one or more C_{1-3}-acyl groups or substituted with amino-groups or C_{1-3}acylamino-groups;

ii) COOH, tetrazole, SO_2NH_2, $SO_2NHCOOR_8$, $CONHR_8$, $NHCOR_8$, where R_8 represents a linear or cyclic C_{1-6} alkyl chain containing one or more polar groups chosen from among the group: OH, NH_2, $NR_{15}R_{16}$, COOH, $CONHR_{12}$, PO_3H, SO_3H, OR_{11} and where R_{15} and R_{16}, which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group, and where R_{11} is a C_{1-3} alkyl or C_{2-4} amino-alkyl chain, R_{12} is a mono-, di-, tri-glycosidic group possibly protected with one or more C_{1-3}acyl groups or substituted with amino-groups or C_{1-3}acylamino-groups or $R_{15}R_{16}$ joined together form with the N-atom a saturated 4-6 membered heterocycle possibly substituted with C_{1-3}alkyl-groups or with saturated 4-6 membered heterocycle-groups containing at least an N-atom;

iii) $COOR_{17}$, $CONHR_{12}$, OR_{12} where R_{12} is a mono-, di- or tri-glycoside group possibly protected with one or more C_{1-3} acyl groups or substituted with amine or C_{1-3} acylamine groups and R_{17} is a group R_{12} as above definined or a group C_{1-3}alkyl, C_{1-3}alkylphenyl, wherein the phenyl-group can be substituted with a group OH, NO_2, NH_2, CN, CH_3, Cl, Br;

R_5, R_6, R_7, which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group; with the proviso that when R_1 and R_2 are benzyl

or 4-hydroxybenzyl then R_3 and R_4 are not isopropyl, their pharmaceutically acceptable salts, their enantiomers and mixture thereof.

2. Compounds according to Claim 1, in which:

f, g, h, m, which may be the same or different from one another, may be 0 or 1;

R_1 and R_2, which may be the same or different from one another, represent the side chain of a natural amino acid chosen from among tryptophan, phenyl alanine, tyrosine, histidine or the side chain of a non-natural amino acid chosen in the group:

tryptophan and phenyl alanine, either mono- or di-substituted with residues chosen from among C_{1-3} alkyl or halo-alkyl, C_{1-3} alkoxyl or amino-alkoxyl, halogen, OH, NH_2, $NR_{13}R_{14}$, where R_{13} and R_{14}, which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group;

R_3 represents a group chosen from among:

- linear or branched alkyl having the formula C_nH_{2n+1}, with n = 1-5 (chosen in the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl) cycloalkyl or alkylcycloalkyl of formula C_nH_{2n-1} with n = 5-9 (chosen in the group consisting of cyclopentyl, cyclohexyl, methylcyclohexyl)
- $(CH_2)_r$-Ar_1, where r = 1 or 2 and where Ar_1 is an aromatic group chosen in the group consisting of: α-naphthyl, β-naphthyl, phenyl, indole, the said Ar_1 group being possibly substituted with a maximum of 2 residues chosen in the group consisting of: C_{1-3} alkyl, CF_3, C_{1-3} alkoxyl, Cl, F, OH, NH_2;

R_4 represents an L-Q group where:

L is a chemical bond or CH_2, and

Q is a group chosen from among:

- OH, NH_2, NR_9R_{10}, OR_{11}, and where R_9 and R_{10}, which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group, C_{1-3}hydroxy alkyl, C_{1-3}dihydroxyalkyl, C_{1-3}alkyl-$CONHR_{12}$ (wherein R_{12} is a monoglycosidic group derived from D or L pentoses or hesoxes (chosen in the group consisting of ribose, arabinose, glucose, galactose, fructose, glucosamine, galactosamine and their N-acetylated derivatives)), C_{1-3}alkyltetrazole, C_{1-3}alkyl-COOH or wherein R_9R_{10} are joined together to form with the N atom a morpholine or a piperidine ring and where R_{11} is a C_{1-3} alkyl chain, or a C_{2-4} amino-alkyl chain;

- $NHCOR_8$ wherein R_8 is a cyclohexane containing from 2 to 4 OH groups, a C_{1-6} alkylchain containing a polar group (chosen in the group consisting of NH_2, COOH, $CONHR_{12}$ (wherein R_{12} is as hereabove define) or [1,4']bipiperidine)
- COOH, $COOR_{17}$ or $CONHR_{12}$, wherein R_{12} is as hereabove defined and R_{17} is as R_{12} or a group 4-nitrobenzyl.
- R_5, R_6, R_7 are H.

in which the carbon atom that carries the substituents R_3 and R_7 has configuration R.

3. Compounds according to Claim 2, as specified below:

Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH-]}

Cyclo{-Suc-Trp-Phe-[(S)-NH-CH($CH_2C_6H_5$)-CH_2-NH-]}

Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_{11}$)-CH_2-NH-]}

Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_4$(4-OCH_3))-CH_2-NH-]}

Cyclo{-Suc-Trp(5F)-Phe-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH-]}

Cyclo{-Suc-Trp(Me)-Phe-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH-]}

Cyclo{-Suc-Phe(3,4-Cl)-Phe-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH-]}

Cyclo{-Suc-Trp-Phe(3,4-Cl)-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH-]}

Cyclo{-Suc-Trp-Tyr-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH-]}

Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_3$-3,4-diCl)-CH_2-NH-]}

Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_4$-4-OH)-CH_2-NH-]}

Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-CH_2-C_6H_5)-CH_2-NH-]}

Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-2-naphthyl)-CH_2-NH-]}

Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-indol-3-yl)-CH_2-NH-]}

Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-5-F-indol-3-yl)-CH_2-NH-]}

Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_4$-3-F)-CH_2-NH-]}

Cyclo{-Suc-Trp-Phe-[(R)NH-CH(CH_2-C_6H_3-3,4-diF-CH_2-NH]-}

Cyclo{-Suc-Trp-Phe-[(R)NH-CH(CH_2-C_6H_4-4-CF_3 -CH_2-NH]-}

Cyclo{-Suc-Trp-Phe-[(R)-NH-CH_2-CH($CH_2C_6H_5$)-NH-]}

Cyclo{-Suc-Trp-Phe-[(S)-NH-CH_2-CH($CH_2C_6H_5$)-NH-]}

Cyclo{-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH-]-$(CH_2)_3CO$-}

Cyclo{-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-N(CH_3)]-$(CH_2)_3CO$-}

Cyclo{-Suc[1(S)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

Cyclo{-Suc[1(R)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

Cyclo{-Suc[2(S)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

Cyclo{-Suc[2(R)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

Cyclo{-Suc[1(S)-NH(CH_3)]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

Cyclo{-Suc[1-COO(CH_2-C_6H_4-4-NO_2)]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

Cyclo{-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH-]}

Cyclo{-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH-]}

Cyclo{-Suc(1-OH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH-]}

Cyclo{-Suc(2-COOH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH-]}

Cyclo{-Suc(2-OH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH-]}

Cyclo{-Suc[1(S)-(2H-tetrazolyl-5-ylmethyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}.TFA

Cyclo{-Suc[1(S)-(morpholin-4-yl)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}.TFA

Cyclo{-Suc[1(S)-N(CH_3)$_2$]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]-}.TFA

Cyclo{-Suc[1(S)-(piperidin-4-yl)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]-}.TFA

Cyclo{-Suc[1(S)-(N(CH_2CH_2OH)$_2$)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}.TFA

Cyclo{-Suc[1(S)-(N($CH_2CH(OH)CH_2OH$)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}.TFA

Cyclo{-Suc[1(S)-(3-carboxypropanoyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}.

Cyclo{-Suc[1(S)-[3-N'-(β-D-glucopiranos-1-yl)-carboxamidopropanoyl]amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}

Cyclo{-Suc[1(S)-[(carboxymethyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-} TFA

Cyclo{-Suc[1(S)-[N'-(β-D-glucopiranos-1-yl)-carboxyamidomethyl]amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-} TFA

Cyclo{-Suc[1(S)-(chinyl)amine]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}

Cyclo{-Suc[1(S)-(4-aminobutanoyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-} TFA

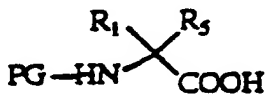
Cyclo{-Suc[1(S)-[(1,4')bipiperidin-1-yl]acetamido]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-} TFA

Cyclo{-Suc[1-N-(β-D-glucopiranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}

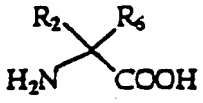
Cyclo{-Suc[1(S)-[N'-(2-N-acetyl-β-D-glucopiranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}.

4. Process for the synthesis of a compound of general formula (I), where X_1, X_2, X_3, X_4 are CONH and the other substituents are as defined in Claim 1, where:

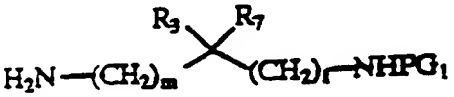
a) the suitably protected amino acids (1), (2) and (4)



(1)

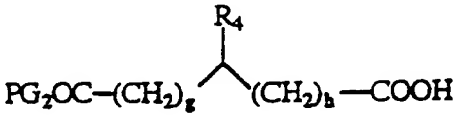


(2)



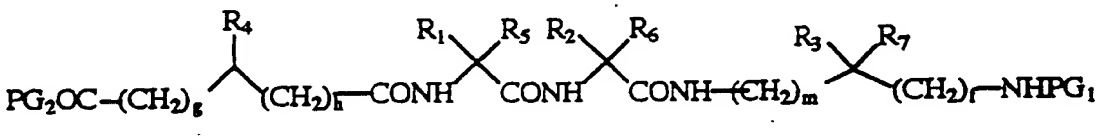
(4)

are made to react, as shown in the diagram, with the derivative of the protected succinic acid (7)



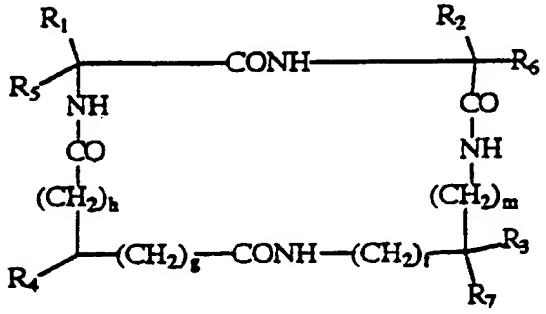
(7)

thus obtaining the linear compound (8)



(8)

b) the linear compound 8, is deprotected and cyclicized to yield the final monocyclic compound (10) of formula (1)



(10).

5. Pharmaceutical compositions containing as active principle the compounds of general formula (I) according to Claim 1 in combination with pharmaceutically acceptable carriers or excipients.

6. Pharmaceutical compositions according to Claim 5, to be used as tachykinin antagonists.

7. Pharmaceutical compositions according to Claim 6, to be used as antagonists of the human NK-2 receptor.

8. Pharmaceutical compositions according to Claim 7, to be used in the treatment of the bronchospastic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and of the ureter during cystitis, and kidney infections and colics.

9. Pharmaceutical compositions according to Claim 7, to be used as anxiolytics.

10. Use of a compound according to Claim 1 as tachykinin antagonist.

11. Use of a compound according to Claim 1 as NK-2 antagonist.

12. Use of a compound according to Claim 1 in the treatment of the bronchospastic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and of the ureter during cystitis, and kidney infections and colics.

13. Use of a composition according to Claim 1 as an NK-2 antagonist for the treatment of anxiety syndromes.

14. Method for the treatment of the bronchospastic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and of the ureter during cystitis, and kidney infections and colics, in which quantities of between 0.02 and 10 mg/kg of body weight of active principle consisting of products of formula (I), according to Claim 1, are administered to the patient.

Add B9

Add a3

Add B10